REMARKS

I. STATUS OF CLAIMS AND EXPLANATION OF AMENDMENTS

A. Status of claims

Claims 1-8, 10-18, and 21-72 were pending in the instant case at the time of the outstanding Office action, and new claims 73-74 have now been added.

Claim 29 stands rejected under 35 U.S.C.§102 (a) and (b), and claims 1-6, 10-18, and 21-72 stand rejected under 35 U.S.C.§103. Claims 7 and 8 have been objected to for depending from a rejected base claim, but have otherwise been deemed allowable.

B. Explanation of amendments

Claims which had recited treating/treatment "to inhibt stenosis or restenosis" of a blood vessel have been amended to recite "to inhibit restenosis."

Claim 22 has been amended to fix a typographical error or ambiguity with respect to a prior amendment.

New claims 73-74 find support throughout the application, including at page 9, lines 24-27.

The Applicants do not intend by these amendments to abandon the subject matter of any claim as previously presented, and reserve the right to pursue such subject matter in related applications, such as continuing applications.

II. INTERVIEW SUMMARY

The Applicants acknowledge with thanks the courtesy extended by Examiner Kaushal to the undersigned attorney during the interview in July, during which the Applicants indicated that they would respond to the Office action with arguments in the nature of those set forth below.

III. THE REJECTION OF CLAIM 29 UNDER 35 U.S.C.§102 SHOULD BE WITHDRAWN

In paragraph 3 of the Office action, the Patent Office rejected claim 29 as allegedly being anticipated by either Alitalo et al. or Achen et al., two references of record. The Applicants respectfully traverse.

Claim 29 recites a kit comprising a containiner containing a VEGF-C and/or VEGF-D polynucleotide and a label attached to or packaged with the container, the label describing use of the agent for inhibition of restenosis of a blood vessel. The Patent Office acknowledges that claim 29 recites a label that is not present in the cited references, but alleges that the label "does not add patentable weight to this invention." (Office action at p. 2.) The Patent Office reasons that the label carries no patentable weight because the function of the polynucleotides does not depend on the printed matter itself, which is, allegedly, not a part of the product or device. "They function equally effectively with or without the instructions." (Office action at p. 4.) The Patent Office also noted that "the instructions do not physically or chemically affect the chemical nature of the components of the kit." (Id.)

At the outset, the Applicants wish to clarify the premise that the polynucleotides function equally effectively with or without the instructions. The polynucleotides do not function *in the container* to treat restenosis. The polynucleotides function to inhibit restenosis when administered according to the invention. A label describing use of the VEGF-C/D agent for inhibition of restenosis embodies a novel feature of the invention.

When printed matter is part of an invention, it is improper to ignore the printed matter in determining patentability. *See In re Gulack,* 703 F.2d 1381, 1385; 217 U.S.P.Q. 401 (Fed. Cir. 1983) ("The Board cannot dissect a claim, excise the printed matter from it and declare the remainng portion of the mutilated claim to be unpatentable.") It is impossible to find the present claims *anticipated* without ignoring the recitation of a label that is not taught in the cited art.

Morevoer, the standard for patentability does not ask whether the non-printed elements "depend on the printed matter" to function or whether the printed matter "affects the chemical nature" of the other components. According to the

Federal Circuit, "the critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate." *Id.* at 1386. The *Gulack* case involved a headband or other band with digits imprinted upon it. The band itself functioned as a band in the absence of the numbers. The court nonetheless found the requisite functional relationship, and reversed the rejection.[1]

The printed matter in claim 29 does recite an unobvious functional relationship in that it directs a medical application for the polynucleotides that was never suggested before. There is no prior art suggesting the use of VEGF-C or VEGF-D agents to inhibit restenosis.

A search of the Patent Office's database of recently issued patents indicates that there is precedent for allowing claims in the biomedical arts where an element of the claim is an instruction label. For example, claims 15-17 of recently issued U.S. Patent 6,475,796 (Exhibit 2) read as follows:

> 15. An article of manufacture comprising a VEGF variant (a) having a cysteine (C) residue at amino acid position 116 substituted by another amino acid, and a glycosylation site at amino acid positions 75-77 removed by site-directed mutagenesis of the encoding nucleic acid, where the amino acid numbering follows the numbering of the 121 amino acids long native human VEGF (hVEGF121) (amino acids 27-147 of SEQ ID NO: 2), (b) having at least 85% sequence identity with the mature hVEGF121 polypeptide (amino acids 27-147 of SEQ ID NO: 2), and (c) having enhanced biological activity relative to said mature hVEGF121 (amino acids 27-147 of SEQ ID NO: 2);
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> a container; and

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[1] In *In re Levin*, 1997 U.S. App. LEXIS 1781 (Fed. Cir. 1997) (Exhibit 1), an unpublished decision not citable as precedent, the court analyzed an invention involving a containiner for a pharmaceutical product and expiration date indicia on the container. The court concluded that this printed matter possessed a legitimate functional relationship because "The color codes expiration date indicia provides information about the substrate or what is contained in the substrate." There was no anticipation, but the involved claims were ultimately rejected as obvious, because the functional relationship was obvious.

a label or package insert comprising instructions for administration of said VEGF variant.

16. The article of manufacture of claim 15 **wherein said instructions concern the treatment of coronary artery disease.**

17. The article of manufacture of claim 16 **wherein said instructions concern the treatment of peripheral arterial disease.**

(Emphasis added.)

Likewise, claim 3 of U.S. Patent 6,451,979 recites, "A kit containing a probe for distinguishing p53 protein levels from SEQ ID NO:3 protein levels **with instructions for measuring said levels in a malignant cell**, wherein the probe is a monoclonal antibody or single chain antibody that specifically binds to SEQ ID NO:3 but not p53." Claim 15 of U.S. Patent NO. 6,447,772 recites, "A kit comprising a vessel containing a composition according to claim 1, **and instructions directing the use of the composition to reduce the symptoms of autism in a human patient.**" These three examples, all taken from patents issued within the last three months, demonstrate that there is nothing inappropriate or unusual about the type of claim that stands rejected in the present case.

For all of the foregoing these reasons, the rejections of claim 29 should be withdrawn.

IV. THE REJECTION OF CLAIMS 1-6, 10-18, 22-32, 49-69, AND 71, 72; AND, 21-51, 57-69, AND 71, 72 UNDER 35 U.S.C.§103(A) SHOULD BE WITHDRAWN

Claims 1-6, 10-18, 22-32, 49-58, 63-69, 71 and 72 stand rejected under 35 U.S.C.§103(a) as being unpatentable over Isner (U.S. Patent No. 5,652,225 (the '225 patent), and U.S. Patent No. 5,830,879 (the '879 patent)) in view of Alitalo. Claims 21-51, 57-69, 71 and 72 stand rejected under 35 U.S.C.§103(a) as being

unpatentable over Isner (the '225 and '879 patent) in view of Achen *et al.* (WO 98/07832). (Office action at paragraphs 4-5.)

The '225 patent purports to disclose a method for the delivery of a nucleic acid to an arterial cell comprising contacting the cell with a hydrophilic polymer incorporating the nucleic acid (See Abstract, Column 2, Line 25-27 of the '255 patent.) A central purpose of the '225 patent is the use of a "hydrophilic polymer incorporating the nucleic acid, thus avoiding the use of a double-balloon or porous balloon catheter..." (Column 2, Line 1-4.)

The '879 patent purports to teach a method for treatment of blood vessels that have been injured in a variety of circumstances. The treatment involves the inducement of reendothelization of the lining of the injured blood vessel with the use of vascular endothelial growth factor (VEGF). The method involves the selecting a human host having an injured blood vessel, administering to the injured blood vessel DNA encoded with the VEGF gene, and the expression of the VEGF gene to induce reendothelization.

As the examiner has acknowledged, the '225 and '879 patents do not mention the use of VEGF-C or VEGF-D nucleic acids or those proteins.

The examiner cites the Alitalo reference as allegedly teaching that VEGF-C may be an inducer of angiogenesis of blood and lymphatic vessels, and in the formation of collateral vessels around critical stenoses and into injured tissues after infection. Achen *et al.* is cited by the examiner as allegedly teaching that VEGF-D stimulates endothelial cell proliferation and angiogenesis.

The examiner alleges that it would have been obvious to one of skill in the art to combine the methods described in the '225 and '879 patents with the teaching in Alitalo because of an alleged equivalence in function between VEGF-C/D and VEGF and because of an alleged equivalence between therapeutic angiogenesis and therapy to prevent restenosis: "[E]xaminer argues that VEGF as taught by Isner is for the formation of new blood vessels. Examiner argues that restenosis is a mechanism of overcoming a blocked artery, that may be accomplished by the formation of new blood vessels to bypass the clogged artery. Therefore, examiner argues in response to applicant's argument that the intended result of restenosis or

new blood vessel formation results in the same end result . . . . One of ordinary skill would have been motivated to make the substitutions because of the teachings in the prior art, and the intended use of by-passing a clogged artery or providing a treatment for restenosis, accomplished by VEGF-C or VEGF-D." (Office Action at pp. 5-6.) The applicants respectfully traverse.

A. The prior art did not consider VEGF-C and -D to be functional equivalents of VEGF

Contrary to what the examiner asserted in the Office Action, the art did not suggest that VEGF-C or VEGF-D were functional equivalents of VEGF or provide a reasonable expectation of success if one were to substitute these molecules for VEGF in any particular *in vivo* treatment method. In fact, the art taught that VEGF-C and VEGF have significantly different structures and perform different functions *in vivo*.

There are significant differences in the sequence of VEGF and both VEGF-C and VEGF-D. Achen, *Proc. Natl. Acad. Sci. USA*, 95, 548-553 (1998), disclosed that the amino acid sequence of VEGF-C and VEGF-D share only a 30 and 31 percent sequence homology with VEGF, respectively. The Examiner has failed to cite any art indicating that this level of sequence similarity is a reliable predictor of function, and has failed to rebut exemplary art cited by the applicants indicating that this level of sequence similarity is not predictive of similar function. (See Amendment of March, 2002, at pp. 5-6.)

Moreover, the art taught that VEGF-C and VEGF-D have their greatest affinity for the Flt4 (VEGFR-3) receptor, and do not exhibit binding for VEGFR-1. In contrast, VEGF has greater affinity for VEGFR-2, and binds VEGFR-1, but exhibits no significant affinity for Flt4 (VEGFR-3). People skilled in the art would not have expected molecules with only a 30 percent sequence homology and different receptor binding profiles to behave identically *in vivo* or be readily substitutable in therapeutic methods with a reasonable expectation of success. In this regard, it is worth observing that VEGFR-3 expression becomes largely restricted to *lymphatic* endothelia in mature mammals. The Alitalo reference cited by the examiner reports that when VEGF-C was expressed under the control of a keratin promoter in

transgenic mice, the mice displayed abundant growth of lymphatic vessels under the skin (where the promoter would have been most active). (See Alitalo at Example 29, pages 88-91.) In contrast, the prior art relating to VEGF and VEGFR-2 largely focuses on their effects on blood vessels. This evidence of divergent function at both the molecular and systemic level provides compelling evidence that the art would not have considered VEGF-C/D to be suitable replacements for VEGF with any reasonable expectation of success. In the absence of a reasonable expectation of success, the rejections for obviousness must be withdrawn.

B. The prior art did not consider the goals of prevention of restenosis and therapeutic angiogenesis to be equivalent.

The rejection is wrongly premised on the an assumption that anti-restenosis therapy and angiogenesis thepary are equivalent goals:

> Examiner argues that VEGF as taught by Isner is for the formation of new blood vessels. Examiner argues that restenosis is a mechanism of overcoming a blocked artery, that may be accomplished by the formation of new blood vessels to by pass the clogged artery.
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> (Office action at p. 5.)

Coupled with an alleged teaching in Alitalo that VEGF-C shares a redundant function with VEGF in the promotion of angiogenesis, the Examiner found an alleged motivation to combine the cited references and reject the claims.

In fact, the art treats the goal of prevention of restenosis (following the re-opening of a blood vessel) to be a medical problem distinct from the goal of promoting neoangiogenesis. Restenosis is a re-narrowing or blockage of an artery at the same site where treatment for stenosis, such as an angioplasty and/or stent procedure, has already taken place. In contrast, angiogenesis is the sprouting of new capillaries from pre-existing vessels characterized by an expansion of the endothelium by proliferation, migration and remodeling. Examination of published scientific and popular literature demonstrates that prevention of restenosis is recognized as a medical goal in its own right for the almost one million angioplasty procedures performed every year in the U.S. (See, e.g., Dangas & Kuepper, *Circulation, 105*: 2585-87 (2002); Chicago Tribune, May 10, 2002, Section 3, p. 4 Exhibits 3 and 4.)

Angiogenesis is a dynamic multistep process, where the process is initiated by vessel destabilization including a weakening of the intercellular contacts between the endothelial cells. (See Exhibit 5, Parfyonova *et al., Biochemistry (Moscow), 67(1)*: 119-134 (2002) at p. 127.) These vesssel-destablizing effects that occur during angiogenesis are not obviously desirable if the goal is prevention of restenosis. Likewise, the "intimal hyperplasia" that characterizes restensosis is characterized by smooth muscle cells, extracellular matrix, and an abundance of new capillaries (Cercek et al., IDS No. C10, at p. 24C, column 2, last paragraph), which would suggest that angiogenic factors could aggrevate, rather than prevent, restenosis. In other words, restenosis has some clinical features of *pathogenic angiogenesis*.

The Patent Office's equating of anti-restenosis and neoangiogenesis is also directly contradicted by the fact that the prior art taught that certain angiogenic factors promote, rather than inhibit, restenosis. For example, platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) are both known promoters of angiogenesis, and these relatives of VEGF are also reported to play a role in *causing* restenosis. See, e.g., Cercek et al., IDS Document C10; Chang et al., IDS Document C11 (p. 186 and Fig. 2); Parfyonova et al. (Exhibit 5) at p. 125.

The literature cited and discussed at pages 3-4 of the Background section of the present application (and of record in the IDS) is further evidence that the solution for restenosis does NOT clearly lie in the administration of angiogenic factors in general, or VEGF in particular.

Thus, rather than suggesting an equivalence in the goals of therapeutic angiogenesis and prevention or restenosis, the prior art teaches away from the analogy that the Patent Office is relying upon for a motivation to combine references.

C. Conclusion

Based on the recognized differences between the medical goals of preventing restenosis and promoting therapeutic angiogenesis, one of ordinary skill in the art would not have been motivated to combine references in the manner suggested by the Patent Office. Even if one did combine such references, there would have been no reasonable expectation from the prior art as a whole that VEGF-C/D could be substituted for VEGF, given the well-documented, substantial differences in amino

acid sequence, receptor binding profile, and *in vivo* effects between VEGF-C/D and VEGF. Even if there were an expectation of "success," the expectation was with respect to Isner's goals of therapeutic angiogenesis and not restenosis. For these and other reasons set forth in response to previous office actions, the rejection of claims 1-6, 10-18, 22-32, 49-58, 63-69, 71 and 72; and 21-51, 57-69, 71, and 72 under 35 U.S.C.§103(a), over Isner (the '225 and '879 patents), in view of Alitalo or Achen, be withdrawn.

V. THE REJECTION OF CLAIMS 1-6, 10-18, AND 22-72 UNDER 35 U.S.C.§103(A) SHOULD BE WITHDRAWN

Claims 1-6, 10-18, and 22-72 stand rejected by the examiner under 35 U.S.C. 103(a) as allegedly obvious in view of Isner in combination with Alitalo (as applied to claims 1-6 and 10-18) or Achen (as applied to claims 21, and 33-48) and further in view of Martin et al. The primary and secondary references are cited as discussed above. The examiner cites Martin et al. for suggesting the use of a particular delivery device.

Martin fails to cure the deficiencies in the primary and secondary references discussed in the preceding section. Thus, this rejection, too, should be withdrawn.

VI. CONCLUSION

Applicants believe all the claims are now in a condition for allowance. Favorable reconsideration of the application is respectfully requested. The examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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